# Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of illnesses with varying histological appearances, but a common physiological pattern of functional disturbances. They usually lead to the gradual loss of lung volume with preserved airflow rates, the reduction of diffusion lung capacity for carbon monoxide and decreased static lung compliance ***(Schwarz et al.,2003).***

Pulmonologists routinely use pulmonary function tests (PFTs) to help guide their care of patients with respiratory disease. spirometry is the most commonly used PFT. However, Spirometric data can only be obtained from subjects who can comply with forced expiratory maneuvers ***(Clement, 2003).***

Impulse Oscillometry (IOS) is an effort independent technique where brief random pressure pulses over a range of oscillating frequencies (generated by a small loudspeaker mounted in series with a pneumotach) are applied during tidal breathing. The pressure flow oscillations are superimposed on the subject's tidal breaths and real-time recordings of pressure and flow are used to provide an estimate of total respiratory system impedance and its two components, resistance and reactance ***(Ortiz & Menendez, 2002).***

The IOS maneuver is increasingly being performed in lung function studies and provides the advantage of requiring only passive cooperation from the subject, who performs quiet tidal breathing. In addition, IOS does not cause respiratory fatigue and is therefore suitable for repeated measurements ***(Carvalhaes-Neto et al., 1995).***

# Aim of the Work

The aim of this work is to compare between impulse oscillometry (IOS) and simple spirometry in patients with interstitial pulmonary diseases.

# Interstitial Lung Disease

**Definition**:

Interstitial lung disease (ILD) refers to a broad range of conditions that have common clinical, physiological, and radiological features. ILD is not one disease, but several diseases that do not necessarily share a common histopathological or pathophysiological basis. By strict definition, ILD involves abnormalities of the interstitium, the potential space between the epithelial and capillary endothelium basement membranes within the alveolus. However, many of the conditions that have been traditionally included under the heading of ILD actually involve other anatomic structures within the lung. For this reason, the more general term "diffuse parenchymal lung disease" (DLPD) is now considered to be preferable, unless the nature of the disease is defined anatomically. However, the term ILD remains in common clinical usage.

**Epidemiology**:

There are limited data that detail the incidence or prevalence of various ILD's. By rough estimate some of the more common ILD's (such as idiopathic pulmonary fibrosis (IPF), sarcoidosis, or occupational lung disease) together affect about 40 individuals per 100,000 population per year. These numbers indicate that ILD isn't common, but about 81,000 individuals are affected by IPF alone in the United States. Although various ILD's can affect individuals of any age, most occur in adults. Some, such as IPF are uncommon under the age of 50 years, and demonstrate increased incidence with each subsequent decade. Other ILD's, such as sarcoidosis and rheumatologic associated ILD, tend to affect younger adults. The age distribution and male : female ratio vary greatly for specific ILD's. The prognosis, choice of therapy, and natural history differ greatly depending on the specific ILD, so

establishing the exact cause of ILD is critical ***(Simonelli, 2000)***.

Diffuse parenchymal lung diseases (DPLDs) comprise a heterogenous group of disorders. Clinical, physiologic, radiographic, and pathologic presentations of patients with these disorders are varied. However, a number of common features justify their inclusion in a single disease category ***(Elliot et al., 2005).***

Fibrosis of the lung occurs as a part of the healing process consequent of many types of lung injury ***(Hay and Turner-Warwick, 1996)***

The general pathologic process that leads to fibrosis includes:

(a) The organization of intra-alveolar exudate and hyaline membrane.
(b) The healing of the granulomatous inflammation.
(c) The response to chronic interstitial edema or inflammation.

***(Kuhn and Askin, 1985).***

Fibrosis may be localized e.g. that results from organization of acute pneumonia, pulmonary infarcts or tuberculosis ***(Heath and Kay, 1985).*** Fibrosis is particularly important when the injury has involved destruction of the alveolar architecture with loss of functional capillary unit ***(Hay and Turner-Warwick, 1996).***

Interstitial pulmonary fibrosis is a pathological increase in the fibrous tissue in the interstitial spaces of the lungs including both, the alveolar and perivascular interstitial spaces ***(Flenly, 1990)***

The diffuse interstitial pulmonary fibrosis affects predominantly but not exclusively, the acinar parts of both lungs ***(Hay and Turner-Warwick, 1996)***

Based on the reaction of the alveolar interstitium to an injury whether distortion, fibrosis, or destruction, the chronic non-malignant disorders of the lower respiratory tract are classified to those producing mainly destruction i.e., destructive lung disorders (which include alpha-1 antitrypsin deficiency and emphysema) and those producing a various combination of fibrosis and distortion with or without minimal destruction, the latter disorders are called interstitial lung disorders (ILDs). So the terms "interstitial lung disease or disorder" and "fibrotic lung disease" are used almost interchangeably***(Crystal and Ferrans, 1991)***.

ILD is a diverse group of disorders classified together because of common clinical, radiological, physiological and pathological features. Most patient present with the insidious onset of exertional breathlessness and a diffuse nodular, reticular or reticulonodular pattern on the chest radiography. Physiological alterations are typically those of a restrictive defect: reduced lung volume and compliance, reduced diffusing capacity, and arterial hypoxaemia that worsens with exercise. The pathology of the interstitial lung disease mainly involves the parenchyma, in most there is an inflammatory cellular infiltration ***(Jackson and Fulmer, 1998).***

Since the interstitial lung diseases are mainly inflammatory disorders of the lower respiratory tract and since the inflammatory reaction takes place predominantly in the interstitium rather than the alveolar spaces, the term "interstitial pneumonia" or "chronic pneumonitis" are sometimes used ***(Crystal et al., 1994).***

Diffuse (interstitial) lung disease includes a wide variety of conditions, individually relatively uncommon, but collectively found in approximately 50 people per 100,000 population. There are over 200 specific diffuse lung diseases including those characterized by fibrosing and granulomatous histopathology. Only some are of known etiology. It has been

suggested that exposure to environmental agents is a major contributory factor in the development of diffuse interstitial lung disease. For example, occupational exposure to beryllium can cause a chronic granulomatous disease that is clinically and histologically indistinguishable from sarcoidosis ***(Imokawa et al., 1997).*** A disease resembling cryptogenic fibrosing alveolitis (CFA) or idiopathic pulmonary fibrosis (IPF) results from asbestos exposure ***(Crystal and Ferrans, 1991),*** and exposure to cobalt may cause interstitial pneumonia and fibrosis ***( Turner-Warwick et al., 1996).*** Other agents that are known to produce diffuse lung disease include some therapeutic drugs, such as amiodarone and radiation. Identified risk factors include exposure to dust ***(Turner-Warwick 1998),*** cigarette smoking, gender, age, and race ***(Fulmer and Crystal, 1989)***, For example, sarcoidosis occurs predominantly in the 30- to 40-year age range and is more aggressive in patients of Afro-Caribbean descent than in Caucasians. In addition, the male to female ratio is 1:1.5. It has been hypothesized that, because not all individuals exposed to a common environment develop the disease and because apparently trivial exposure to common environmental agents can result in disease, genetics may play a role ***(Elliot et al., 2005).***

**Anatomy of the Alveolar Interstitium:**

The alveolar interstitium is a thin layer of tissue in the alveolar wall formed of:

(1) Epithelial and endothelial basement membrane.
(2) Connective tissue sheet.
(3) Mesenchymal cells.
(4) Inflammatory cells and other molecules.

***(Reynolds, 1988).***

Alveolar interstitium concerns the tissue between the epithelial and endothelial basement membranes. The interstitium of the alveolar wall is in continuity with the connective tissue surrounding the blood vessels. The alveolar

interstitium contains fibroblasts and extracellular matrix, that together represent almost 50% of the tissue volume of the alveolar wall ***(Turner-Warwick et al., 1996).***

The basement membrane is composed of more than 50 different proteins as: Collagen type IV, Lammine which binds the cells of basement membrane, Heparin sulfate, proteoglycans and Nidogan. The basement membrane is formed of 2 layers, lamina lucida and lamina densa ***(Rennard and Crystal, 1992).***

The most abundant interstitial matrix components are collagen type I and III, which are structural macromolecules, normally present in a ratio 2:1. Fibrils composed mostly of type I collagen are thick, whereas fibrils rich in type III collagen are thinner. In addition to collagen, the interstitial matrix includes elastin, proteoglycans, and fibronectin ***(Raghu et al., 1988).***

Proteoglycans are chemotactic factors which act as component factors for mesenchymal cell growth, also as link between intra-alveolar fibrin and fibroblast. This action enhances intra alveolar fibrosis. Fibronectin, which is a glycoprotein has ability to interact with cells and collagen type I.

The membrane of the mesenchymal cells of the connective tissue matrix include fibroblasts, myofibroblasts, pericytes, muscle cells myofibroblast like cells and others. ***(Crystal and Ferrans, 1991)***

The fibroblasts account for 37% of all parenchymal cells and occupy approximately two thirds of the volume of the interstitium ***(Crystal et al., 1994).***

In addition to fibroblasts, mononuclear phagocytes, and lymphocytes are usually present. Although, the basement

membranes determine the topography of their respective cell types, the fibroblasts and interstitial connective tissue matrix provide the structural framework that defines alveolar shape and to a large extent the mechanical properties that modulate the volume – pressure characteristic of the lung during respiration. The integrity of the alveolar wall is essential for the normal function of the pulmonary interstitium ***(Hoogsteden and Van-Hal, 1990).***

The role of macrophage is to defend the respiratory tract from inhaled organisms and also phagocytose particulates that are not opsonized ***(Crystal and Ferrans, 1991).*** Other 10% is made up by T and B lymphocyte ***(Hunninghake and Kalica, 1995).***

Other components as lipids, carbohydrates, proteins, small solutes are filterd from plasma into interstitium. The same is Alpha-1 antitrypsin which is the most potent antielastase ***(Crystal and Ferrans, 1991).***

**Parenchymal cells:**

***Alveolar epithelial cells:***

1) Type I pneumocytes: They are large cells with flattened cytoplasm and few organelles and dependent upon perinuclear portion.
2) Type II pneumocytes(granular).

**Table (1) : Alveolar epithelial cells which line air spaces are 2 types:**

| Type I pneumocyte | Type II pneumocyte |
|---|---|
| ● 30% of alveolar epithelium, cover 90% of the surface area.<br>● Large cell with flattened cytoplasm (membranous).<br>● Lesser capacity for division and longer turnover time. | ● cuboidal.<br>● Has lamellar bodies (granular).<br>● source of pulmonary surfactant.<br>● Greater capacity for division (shorter Turnover).<br>● Proliferates and replaces type I when it is destroyed. |

***(Heath and Kay, 1985)***

The pulmonary capillaries form a branching network of tubes that weave through the interior of the alveolar walls. The capillaries comprise a single layer of endothelial cells lying on a continuous basement membrane ***(Crystal and Ferrans, 1991).***

Although, the endothelial and epithelial basement membranes are distinct structures, they are just at the location where the capillaries come closest to the air spaces, these are the sites of gas exchange ***(Robbins et al., 1999).***

**Table (2): Classification of interstitial lung diseases:**

| Known cause | Unknown cause |
|---|---|
| 1- Inhalents:<br>a) Inorganic dusts/pneumoconiosis (silicosis, asbestosis, hard metal lung/giant cell pneumonitis (GIP).<br>b) Organic dusts (hypersensitivity pneumonitis).<br>c) Gases (oxygen toxicity, sulfur dioxide).<br>2- Drugs and Toxins:<br>a) Chemotherapeutics (bleomycin).<br>b) Antibiotics (nitrofurantoin).<br>c) Toxins (paraquat).<br>3-Infections:<br>a) Viruses (CMV)<br>b) Bacteria (TB)<br>c) Fungi (pneumocystis carinii) | 1-The idiopathic interstitial pneumonias.<br>a) Usual interstitial pneumonitis (UIP) b) Desquamative interstitial pneumonitis (DIP)<br>c) Idiopathic bronchiolitis obliterans organizing pneumonia (BOOP)<br>cytogenic organizing pneumonia (COP)<br>d) Respiratory bronchiolitis associated interstitial lung disease (RBILD)<br>e) Nonspecific interstitial pneumonia (NSIP)<br>f) Lymphocytic interstitial pneumonia (LIP)<br>g) Acute interstitial pneumonia (Hamman Rich Syndrome)<br>2- Connective tissue disease associated ILD<br>Sarcoidosis<br>Eosinophilic granuloma<br>Eosinophilic pneumonia<br>Pulmonary hemorrhage |

***(Boag, 2001)***

## Pathogenesis of Interstitial Lung Diseases

Fibrotic lung disorders are inflammatory diseases in which inflammatory processes in the lower respiratory tract injure the lung and modulate the proliferation of mesenchymal cells, that forms the basis of the fibrotic scar ***(Costabel et al., 1995).***

A common pathogenic sequence underlies most interstitial lung diseases regardless of the etiology. As the development of the pulmonary fibrosis is thought to follow injury of the alveolar wall via either (1) the vasculature (2) or the airways. Following this injury, there is an influx of inflammatory and immune effector cells ***(Selman et al., 2001).***

Each of the interstitial disorders seems to follow the same general scheme of pathogenesis through stages of:
1-Alveolitis.
2-Derangement of alveolar capillary units.
3-End stage pulmonary fibrosis.
***(Hunninghake and Crystal, 1991).***

The alveolitis of the interstitial lung disorders is likely the controlling factor in the pathogenesis of the interstitial lung diseases. The rate, the form and the extent of the derangement caused by the alveolitis appear to be a function of the number, type and state of activation of effector cells comprising it ***(Crystal et al., 1994).***

Reversibility of the interstitial lung diseases seems to be controlled by the relative permenante of the derangement caused by the alveolitis ***(Weinberger and Crystal, 1989).*** This permenante appears to be modulated at least in point by the relative integrity of the epithelial and endothelial basement membrane ***(Varko, 1985).***

The alveolitis stage is remarkably different from disease to disease. Normally the inflammatory and immune effector cells of the lung parenchyma are dominated by the alveolar macrophage, which generally comprises at least 90 percent of the effector cells present ***(Hunninghake and Kalica, 1995)***

Macrophages are found on both, the alveolar epithelial surface and within the interstitium, but are relatively more abundant on the epithelial surface ***(Flaherty and Martinez, 1977).***

Alveolar macrophages are derived from blood monocyte but can replicate in situ from a reservoir of cells within the interstitium ***(Admason and Bowden, 1989).***

The alveolar macrophages is thought to direct the alveolitis by virtue of its ability when activated to:

1) Modulate both the local accumulation and the replication of the interstitial fibroblast.
2) Regulate lymphocyte response.

These effects are mediated via what is called "inflammatory or immune mediator"

***(Crystal et al., 1994).***

**Important mediators are:**

**{1} Fibronectin:**

Fibronectin acts not only as a chemotactic factor for fibroblasts mediating their recruitment at sites of tissue injury ***(Rennard, 1991).*** but also as competence factor initiating fibroblast replication process ***(Turner-Warwick, 1998).***

**{2} Alveolar macrophage derived growth factor(AMDGF):**

Alveolar macrophage derived growth factor(AMDGF) is an 18,000 dalton protein produced only by activated macrophages and act as progression factor which stimulates fibroblasts to proceed through the cell cycle and proliferate ***(Crystal and Ferrans, 1991).*** This is activated by inducing fibronectin primed fibroblasts to release an insulin-like growth factor which signals the same or near by fibroblast to replicate ***(Bitterman et al., 1991).***

**{3} Immune interferon** ***(Hunninghake and Kalica, 1995).***

**{4} Platelate-derived growth factor(PDGF)** ***(Kovacs, 2001)***

**{5} Interleukin 1(IL-1) particularly interleukin 1B :**which maintains and modulates active inflammation and fibrosis in the lung ***(Yamaguchi et al., 1988).***

**{6} Interleukin-1-receptor antagonist (IL-1ra):** is a recently described member of pulmonary cytokines family which inhibits (IL-1), also is produced by alveolar macrophage. Thus the total amount of IL-1 activity is related to the relative amount of both IL-I and IL-Ira. ***(Moore et al., 1992).***

Lymphocyte is the next most popular effector cell of the lower respiratory tract. It is present more within the interstitium than on the epithelial surface ***(Reynolds, 1988).*** Approximately 73 percent are T lymphocytes of which 6 percent are activated ***(Hunninghake and Kalica, 1995).***

Activated T lymphocytes secrete lymphokines (e.g. macrophage migration inhibition factor, leukocyte inhibitory factor and monocyte chemotactic factor) which regulate the traffic and function of other inflammatory and immune effector cells ***(Moore et al., 1992).***

Eight percent are B lymphocytes, of these B lymphocytes 0.1 to 0.3 percent are secreting immunoglobulin G (IgG) and immunoglobulin M (IgM). The remainder of cells are null cells ***(Lawrence et al., 1980).***

Polymorphonuclear leukocytes are rare in the alveolar structures which is an important concept regarding the normal maintenance of lung homeostasis. These cells are capable of releasing a variety of mediators that have the potential to markedly derange the alveolar structures. Neutrophil is the best studied cell. It can release collagenase, elastase, neutral protease, acid protease, B glucuronidase and various oxidants. All of which are hazardous to the cellular and non cellular constituents of the lung parenchyma ***(Crystal and Ferrans, 1991).***

There are two types of alveolitis that are commonly found in the interstitial lung disorders:

1- The macrophage-lymphocyte type: which is characterized by relatively more lymphocytes than macrophages and generally found with granulomas e.g sarcoidosis and hypersensitivity pneumonitis, this type is termed a"lymphocyte alveolitis".

2- Macrophage-lymphocyte-neutrophil type: which is dominated by the macrophage, but it most remarkable for the presence of neutrophils e.g idiopathic pulmonary fibrosis. This type of alveolitis is commonly called"neutrophil alveolitis".

***(Rosen et al., 2000).***

***Maintenance of the alveolitis of the interstitial lung disorders:***

The interstitial lung disorders are unique among lung diseases in that the alterations in the inflammatory and immune effector cells of the alveolar structures are choronic alteration ***(Crystal et al., 1994).***

The chronic alveolitis of the interstitial lung disorders presents a continual burden of immunoglobulins, oxidants and proteolytic enzymes that overcomes the protective measures of the lower respiratory tract ***(Hunninghake and Kalica, 1995).***

In idiopathic pulmonary fibrosis (IPF), the resident cell that regulates neutrophil traffic is likely the alveolar macrophage when subjected to appropriate stimuli, the alveolar macrophage release a low molecular weight factor partially lipid in nature which is chemotactic for neutrophils ***(Valone et al., 1989).***

One possible mechanism for the inhibition and maintenance of the alveolitis of IPF is the persistent presence of immune complexes within the alveolar structures, which are found in the serum, and lung of these patients, also on their

alveolar macrophages ***(Hunninghake and Kalica, 1995).*** Since immune complexes are the agent that stimulates macrophages to release neutrophil chemotactic factor. The neutrophils release mediators and active collagenase which are found in 70% of patients with IPF. The active collagenase is a critical factor in the pathogenesis of the disease ***(Gadek et al., 1989).***

In chronic hypersensitivity pneumonitis. The inhibition of a complex, proteinaceous antigen is associated with the localization of T-lymphocytes within the alveolar structures ***(Reynolds, 1988).***

These lymphocytes have been shown to release antigen specific lymphokines, that have the potential to regulate the traffic of mononuclear phagocytes within the alveolar structures ***(Schuyler et al., 1988).***

Other cells that play a role in the pathogenesis of lung fobrosis as:

**Mast cell:** which

**(1)** Releases a variety of cytokines, lipid derived mediators, amines, proteases and proteoglycans. All of which can regulate adjacent cells and the metabolism of the extracellular matrix of connective tissue ***(Steven and Austen, 1989).***

**(2)** Influences multiple phenotypic characteristics of fibroblasts including their movement ***(Ginsburg et al., 1993),*** functional activity ***(Subba et al., 1993)*** and proliferation ***(Dayton et al., 1999).***

**Eosinophils:** are implicated in the pathogenesis of lung fibrosis in interstitial lung diseases ***(Crystal, 1997).*** As there is an interrelationship between neutrophils, eosinophils and mast cell which suggests that mast cell activation may be the initiation of mast cell granulocyte cascade, in which mast cell

derived cytokines contribute to an influx of neutrophils and eosinophils which in turn provides additional cytokines activities important to the progression of the response ***(Crystal et al., 1994).***

The fibrogenic process proceeds not only within the interstitium but also intra-alveolar. For fibroblast to reach the intra-alveolar exudates, the epithelial basement membrane must be damaged, a process conducted by neutrophilic proteases ***(Crystal et al., 1994).*** The organized intra-alveolar exudate is then incorporated within the alveolar wall by migration of proliferating type II pneumocytes on the surface of the organized buds ***(Spencer, 1985).*** Intra-alveolar fibrosis also reflects the inefficiency of phagocytic cells to remove acute inflammatory exudates ***(Turner-Warwick, 1998).***

As the fibrosis being a healing process, the more damage is affecting the alveolar walls, the more fibrosis results.

The damage to the alveolar architecture is produced to a large extent by the inflammation secondary to an injurious process. The intensity and the state of activation of the inflammatory and immune effector cells on one hand and the state of the defense mechanism on the other hand determine the degree of the resultant fibrosis ***(Keogh and Crystal, 1989); (Crystal and Ferrans, 1991) and (Crystal, 1997).***

Fibrosis of the alveolar walls is characterized by an expansion of the alveolar interstitium, with an increase in the number of fibroblasts and quantities of fibroblast products, particularly type I collagen ***(Crystal, 1997).*** This accumulation of type I collagen within the alveolar wall likely results from a shift in the relative proportions of parenchymal cells comprising the alveolar structure. The key change is the marked increase in the members of fibroblasts, which are the